CLINICAL PRACTICE

Exanthematous Drug Eruptions

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A 50-year-old woman with bipolar depression presents with a widespread pruritic rash of 1 day's duration. She is afebrile and otherwise well. She has a history of childhood eczema and is allergic to sulfonamide antibiotics. Her medications include thyroxine daily, naproxen intermittently, and lamotrigine, which she began taking 3 weeks earlier. How should this case be evaluated and treated?

THE CLINICAL PROBLEM

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In the United States, patients fill more than 300 million drug prescriptions and purchase millions of over-the-counter medications each month.[1] In many cases patients are using these medications for the first time. Cutaneous reactions are among the most common adverse effects of drugs, including penicillins, cephalosporins, sulfonamide antimicrobial agents, and allopurinol (with an incidence of up to 50 cases per 1000 new users), and particularly the aromatic amine antiseizure medications, including carbamazepine, phenytoin, and lamotrigine (with an incidence of up to 100 cases per 1000 new users).[2-7] Drug-related rash is reported for nearly all prescription medications, usually at rates exceeding 10 cases per 1000 new users. These reactions can range from asymptomatic mild eruptions to life-threatening conditions. Cutaneous reactions may be difficult to distinguish from common rashes that are unrelated to medication use, particularly viral exanthems.

Exanthematous drug eruptions (also called morbilliform or maculopapular drug eruptions) are the most common drug-induced eruptions.[2,7] They and the much rarer and more serious Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP), and drug reaction with eosinophilia and systemic symptoms (DRESS) are idiosyncratic, T-cell–mediated, delayed (type IV) hypersensitivity reactions.[8-11] Classically, antigen-presenting cells present haptens, composed of the drug or its metabolite bound to a protein or peptide, to naive T cells. These antigen-specific T cells proliferate, infiltrate the skin, and release cytokines, chemokines, and other proinflammatory mediators that are responsible for the signs and symptoms of the drug-related rash.[12-15] According to an alternative theory known as the p-i (pharmacologic interaction of drugs with immune receptors) concept, small-molecule drugs or their metabolites, which are not complete antigens, activate T cells directly by binding to T-cell receptors.[12,13] Irrespective of the mechanism that elicits a T-cell response to a drug, it is not known why only a minority of patients receiving a given drug have a clinical reaction to it, whereas others have immunologic reactivity without a rash.

Alterations in a patient's immune status, as well as genetic factors related to immune response, affect the risk of these drug reactions. Patients with human immunodeficiency virus (HIV) infection, bone marrow transplants, or certain infections

KEY CLINICAL POINTS

EXANTHEMATOUS DRUG ERUPTIONS

- Exanthematous drug eruptions, also called morbilliform or maculopapular drug rashes, occur in 1 to 5% of first-time users of most drugs.
- These often pruritic skin reactions typically appear 4 to 21 days after a person starts taking the causative medication and are characterized by symmetrically distributed, pink-to-red macules and papules that spread rapidly and may coalesce.
- Patients with human immunodeficiency virus infection or bone marrow transplants are at increased risk.
- Identifying and discontinuing the causative drug are the most important steps in management; symptomatic treatment with antipruritic agents and potent topical glucocorticoids may be helpful.
- Signs and symptoms that should alert the clinician to the possibility of a severe cutaneous reaction include mucous-membrane involvement, temperature above 38.5°C, blisters, facial edema and erythema, and lymphadenopathy.

for which they are taking particular medications are at especially high risk.[16,17] For example, most patients with infectious mononucleosis who are being treated with aminopenicillins have exanthematous eruptions, as compared with about 5% of patients without this disorder who are taking these drugs. Certain HLA alleles confer a much higher risk of some T-cell–mediated hypersensitivity reactions. Most often described in cases of severe cutaneous reactions, these associations are generally specific to the type of reaction, causative drug, and ethnic group (see Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[18] In Europeans taking carbamazepine, HLA-A*3101 is reported to be associated with an increased risk of maculopapular exanthems.[19]

Most rashes due to medications are self-limited and only mildly symptomatic. The majority of skin events attributed to drugs are either exanthematous (maculopapular or morbilliform) eruptions (>80%) or urticaria (5 to 10%), but these percentages vary among medications and among patient groups.[2,5,20] Among patients who are not immunologically compromised, severe cutaneous reactions to medications are rare (with an incidence of <1 case per 1000 new users), even with high-risk medications.[8-11,20-23]

Exanthematous eruptions present as a widespread, symmetrically distributed rash composed of pink-to-red macules and papules that may coalesce to form plaques (Fig. 1A, 1B, and 1C). Although mucous membranes are usually spared, redness without blistering may occur at these sites. Pruritus is frequent but highly variable in severity, and low-grade fever (temperature of <38.5°C) is common.

Urticaria (Fig. 1D), photosensitivity, and fixed drug eruptions account for most of the remaining drug-associated eruptions in ambulatory patients. Urticaria shares pathophysiologic features with anaphylaxis and angioedema, both of which may be life-threatening. With most drugs, urticaria is an IgE–mediated, immediate (type I) hypersensitivity reaction. Urticaria due to nonsteroidal antiinflammatory drugs (NSAIDs) or angiotensin-converting–enzyme inhibitors usually reflects the pharmacologic effects of these medications rather than an immunologic reaction.[24-26]

Photosensitivity eruptions that accompany the use of systemic medications are almost always a consequence of ultraviolet- or visible-light activation of a drug, resulting in phototoxic injury to cells in the skin and a sunburn-like reaction that may blister in exposed areas[27] (Fig. 1E). Drugs commonly associated with phototoxicity include tetracyclines (particularly doxycycline), thiazide diuretics, quinolones, voriconazole, vemurafenib, amiodarone, and psoralens.[28]

Fixed drug eruptions present as small (usually <8 cm in diameter), red, round plaques that may sting, usually result in long-lasting pigmentation, particularly in persons with more skin pigment, and typically recur at the same sites (lips, genitalia, and acral skin) on reexposure to the causative medication (Fig. 1F).[29] Commonly responsible drugs include penicillins, NSAIDs, and acetaminophen.[30]

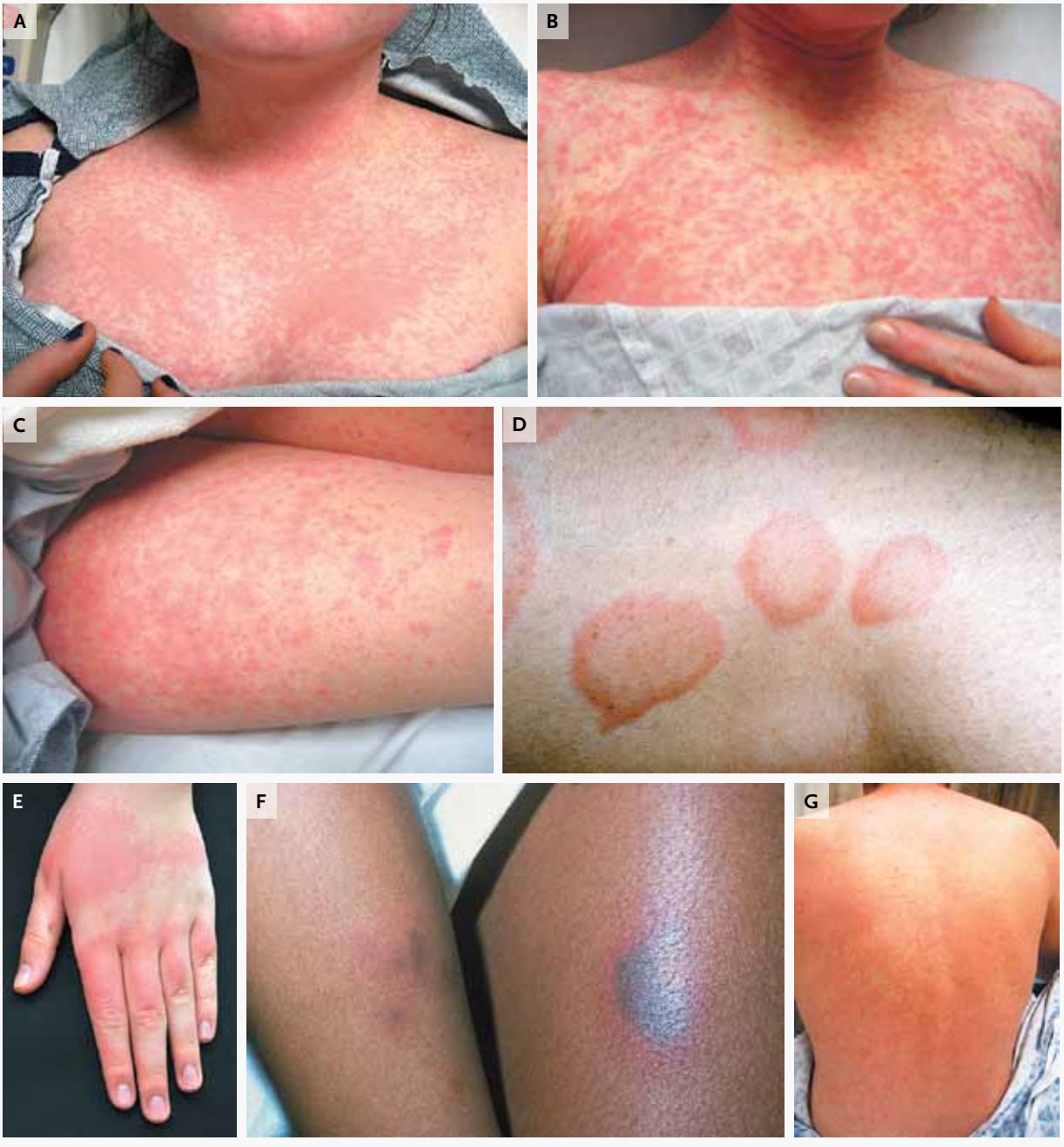

Figure 1. Clinical Presentations of Common Drug Reactions and Measles.

Panels A and B show exanthematous drug eruptions with macules and papules that vary in size and coalesce to form plaques. The eruption shown in Panel A is relatively mild, with symmetric pink macules and papules, whereas the eruption shown in Panel B is more intense, with lesions that are deeper red and more indurated. Panel C shows an exanthematous drug reaction involving the thighs, with red macules and papules coalescing to form plaques and, as is usual, greater proximal involvement. Panel D shows urticaria with characteristic central blanching and red rims. Individual lesions last less than 24 hours. Panel E shows a phototoxic reaction to doxycycline. The sunburn-like reaction is limited to sun-exposed areas in a rower whose knuckles were protected with tape. Panel F shows a fixed drug eruption with hyperpigmentation from prior reactions and at the same sites erythema due to reexposure to the causative drug. Panel G shows measles with pink macules and papules coalescing to form plaques in a patient who had received only a single dose of vaccine.

Table 1. Selected Infections and Other Conditions that Often Include an Exanthem and Characteristics that Help Differentiate Them from an Exanthematous Drug Eruption.*

Diagnosis	Description and Distinguishing Features
Measles (rubeola)	The rash is morbilliform (meaning "measles-like"), a term often used to describe exanthematous drug eruptions, and is usually itchy. Unlike most drug eruptions, the rash seen in measles often begins on the head and neck and spreads rapidly. It usually begins a few days after the onset of fever, cough, coryza, and conjunctivitis. White spots on the buccal mucosa (Koplik's spots) help establish the diagnosis. Typical or atypical rash may occur in previously vaccinated adults, principally those who received only older, killed vaccine or who were incompletely vaccinated.
Rubella	Symptoms are usually milder than those seen in measles, with a similar rash that usually resolves within 3 or 4 days. The rash is often accompanied by fever, adenopathy, and arthralgias.
Roseola infantum (exanthem subitum)	Young children have a high temperature for 3 to 5 days; it usually resolves around the time of onset of the rash, a pink, short-lived eruption. Human herpesvirus 6 is the most frequent cause. Adults have cervical adenopathy, with variable rash and fever that may last for months. The rash usually starts on the trunk and spreads to the face and extremities.
Erythema infectiosum (fifth disease)	In young children, fever (with characteristic "slapped cheeks") develops 2 to 4 days before generalized rash, which begins on proximal extremities and spreads both centrally and peripherally. In adults, arthralgias, which may persist for many weeks, and fever are prominent. The rash often has a livedo pattern. Facial involvement is less prominent in adults than in children. The disease is caused by parvovirus B19.
Infectious mononucleosis	In adolescents and adults, rash is usually associated with aminopenicillin administration, with an onset within 3 days after administration (a more rapid onset than is usual for drug eruptions). Patients are unlikely to have rash with readministration of aminopenicillin after recovery.
Acute graft-versus-host disease	The rash typically occurs 2 to 4 weeks after transplantation. It may be pruritic. If generalized, the rash is often difficult to distinguish clinically from an exanthematous drug eruption.
Acute human immunodeficiency virus seroconversion	The rash has an acute onset 1 to 6 weeks after infection and is usually accompanied by fever, malaise, myalgias, arthralgias, and lymphadenopathy. It is a symmetric exanthematous rash that involves the face, palms, and soles. Oral and genital aphthous-type ulcers may occur.
Other viral exanthems	Causative agents include echoviruses, coxsackie virus, togavirus, and others.

* Other diagnostic aids may include viral culture, skin biopsy, detection of virus by means of polymerase-chain-reaction assay, and serologic tests for antibodies (especially IgM antibody in acute infections).

STRATEGIES AND EVIDENCE

EVALUATION AND DIAGNOSIS

In evaluating a patient with a new rash, the clinician should attempt to determine whether the rash is drug-related, whether it is likely to become severe, which medication or medications are most likely to be responsible, which medications can be discontinued, how the eruption should be treated, and what the patient should be told about future medication use. The appearance of the rash (its distribution and morphologic features and whether mucous membranes are involved), the time of its onset relative to the use of drugs, and an assessment of the patient for the presence of fever and other associated symptoms and signs (indicating involvement of other organs) and past reactions to medications, as well as other characteristics of the patient and any coexisting disorders, should guide decision making.

Any new, symmetric exanthematous eruption may be related to medication. Viral exanthems are often difficult to differentiate from drug-induced exanthems (Fig. 1G). Viral illnesses are often characterized by the rapid onset of widespread, symmetric eruptions of pink-to-red macules and papules that may coalesce, with fever, malaise, sore throat, and conjunctivitis; however, these features may also be seen with a drug eruption. Viral exanthems are more common in children than in adults and are usually self-limited and mildly symptomatic.[31] Table 1 describes the characteristic features of some common viral exanthems that help distinguish them from drug eruptions. Patients with fever, sore throat, or malaise due to infections use many medications (particularly antibiotics and NSAIDs) that also cause exanthematous rash. Because of the time required for hypersensitivity to develop in a patient not previously sensitized to a particular drug, a rash that appears within 3 days after the drug has been initiated for these indications is more likely to be due to infection than to the drug.[2,14,22]

Table 2. Features of Selected Severe Cutaneous Adverse Reactions to Drugs.

Feature	Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)	Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis (SJS–TEN)	Acute Generalized Exanthematous Pustulosis (AGEP)
Clinical features			
Rash	Widespread rash (involving >50% of body-surface area), often exanthematous, and very inflamed; may have other morphologic features, including erythroderma; facial edema and erythema; exanthematous eruption may become purpuric, especially on lower legs	Severe, acute blistering; initially, rash may be macular erythema or exanthematous eruption and trunk lesions predominate; individual lesions may include "spots" and flat, atypical target lesions but not true target lesions characteristic of erythema multiforme, which is not usually drug-related; Nikolsky's sign (ready removal of the epidermis with slight tangential pressure); diagnosis depends on extent of epidermal necrosis according to body-surface area: 10 to 30% in SJS–TEN versus less than 10% in SJS and more than 30% in TEN	Rapid evolution (over a period of hours) of sterile, nonfollicular pustules on erythematous swollen skin; accentuation of rash in body folds; facial edema
Mucosal involvement	Mucosal involvement infrequent	Mucous membranes nearly always involved with blisters and erosions	Mucosal involvement rare
Onset of rash	Onset of rash often >14 days after first dose of drug, especially in the case of antiepileptic agents; for most other drugs, onset 4 to 21 days after first dose	Onset 4 to 21 days after first dose of drug	Initial onset (<3 days) after first dose of an antibiotic but slower onset with other drugs
Other features	Temperature >38.5°C, malaise, lymphadenopathy, involvement of at least one internal organ: liver (in >80% of cases), kidney, muscle, lung, heart, pancreas	Temperature >38.5°C, malaise, sore throat, dysphagia, dysuria, or photophobia initially	Temperature >38.5°C
Laboratory findings	Eosinophilia ($\geq 700\times10^6$ per liter or ≥10% if white-cell count $<4000\times10^6$ per liter) and lymphocytosis or lymphopenia, atypical lymphocytes, thrombocytopenia; simultaneous activation of latent or new infection with human herpesvirus 6 common (not a routine test)	Epidermal necrosis on skin biopsy, with full-thickness loss of epidermis	Leukocytosis with neutrophilia (absolute count, $>7000\times10^6$ per liter)
Relation to medication	By definition, all cases drug-related	80% of cases drug-related	50% of cases drug-related
Differential diagnosis	Systemic lupus erythematosus, mycoplasma infection, viral hepatitis, infectious mononucleosis, other infections	Autoimmune blistering diseases: pemphigus and pemphigoid, acute phototoxicity, staphylococcal scalded skin syndrome	Psoriasis (shares many features with pustular psoriasis)

Most drug-induced exanthematous eruptions evolve rapidly, are symmetric and widespread, reach the maximal extent within 2 days after the elimination of the causative drug, and fade within a week after the drug is eliminated. Some drug eruptions start to fade even while the patient is still taking the causative agent. The character of the individual lesions frequently varies according to the body site (e.g., confluent red plaques on the trunk and discrete pink macules and papules on the extremities). The rash is likely to be a deeper red and may even become purpuric in dependent areas. With the exception of patients who bleed easily, one should be able to cause blanching of the rash in nondependent areas. Skin eruptions that differ in appearance from exanthematous drug eruptions are common in patients treated with tyrosine kinase inhibitors (papulopustular eruptions) and patients with hepatitis C who are treated with telaprevir, interferon alfa, and ribavirin (eczematous eruptions).[32,33]

First-time exanthematous drug eruptions and T-cell–mediated severe cutaneous reactions typically begin to appear 4 to 21 days after the start of treatment with the responsible medication but may develop later in DRESS (Table 2).[2,11,22,23] Therefore, assessment of the timing of drug administration relative to the onset of rash and other symptoms is a key step. Resolution after a medication is stopped (known as a "dechallenge") also helps identify the causative agent.

Since the likelihood of a drug-induced rash varies according to the medication, the population treated, and the indication for use, such factors should be considered in assessing the probability that the patient's rash is due to a specific drug. Aside from the genetic and disease factors discussed above, some groups of patients are at greatly increased risk for unknown reasons. For example, the rate of drug-related rash among young women treated with the antibiotic gemifloxacin (>20%) is about 10 times as high as the rate among other patients treated for the same indications.[34] Organ-specific algorithms rather than algorithms that assess drug causality irrespective of the affected organ system may improve interrater reliability in the assessment of the cause of drug eruptions.[35] Table S2 in the Supplementary Appendix provides an algorithm, adapted from one validated for SJS–TEN (another T-cell–mediated drug reaction), that may help identify the causative drug in cases of exanthematous drug eruptions,[36] although it has not been validated for exanthematous reactions.

ASSESSING THE LIKELIHOOD OF A SEVERE REACTION

It is important to determine whether an exanthematous drug-induced rash is likely to be an early sign of a severe cutaneous reaction. Determining whether DRESS will develop in a patient with a widespread eruption and fever is particularly challenging. Table 2 summarizes the signs and symptoms associated with medication use for the three severe cutaneous reactions that together account for more than 90% of such reactions: DRESS (Fig. 2A), SJS–TEN (Fig. 2B), and AGEP (Fig. 2C). Table S1 in the Supplementary Appendix lists selected medications commonly associated with these reactions, as well as genetic risk factors.

Cutaneous leukocytoclastic vasculitis is characterized by erythematous and purpuric papules predominantly on the lower extremities (Fig. 2D). Although most cases are associated with infection or autoimmune disorders, about 20% are due to drugs.[37] More than 100 drugs have been implicated, particularly propylthiouracil.[38]

Serum sickness–like reactions have a variety of cutaneous manifestations, including exanthematous and urticarial eruptions, as well as fever, lymphadenopathy, arthralgia, and inflammation of other organs. Foreign proteins, including biologic agents, minocycline, and cephalosporins, have been associated with these reactions.

FURTHER EVALUATION

In most cases of exanthematous drug reactions, a structured clinical evaluation will identify the most likely causative drug (or drugs), which can be withdrawn and avoided in the future (Table S2 in the Supplementary Appendix). Occasionally, greater certainty is needed to establish the causative drug. Whereas in vitro detection of specific IgE antibodies may assist in identifying cases of urticaria, angioedema, and anaphylaxis due to beta-lactam antibiotics and some other drugs, these tests are not relevant to T-cell–mediated drug eruptions, including DRESS and SJS–TEN.[39]

Various tests have been advocated for establishing the causative drug in cases of exanthematous eruption, but all the tests have limitations. Patch testing has long been used to document the cause of allergic contact dermatitis, a T-cell–mediated

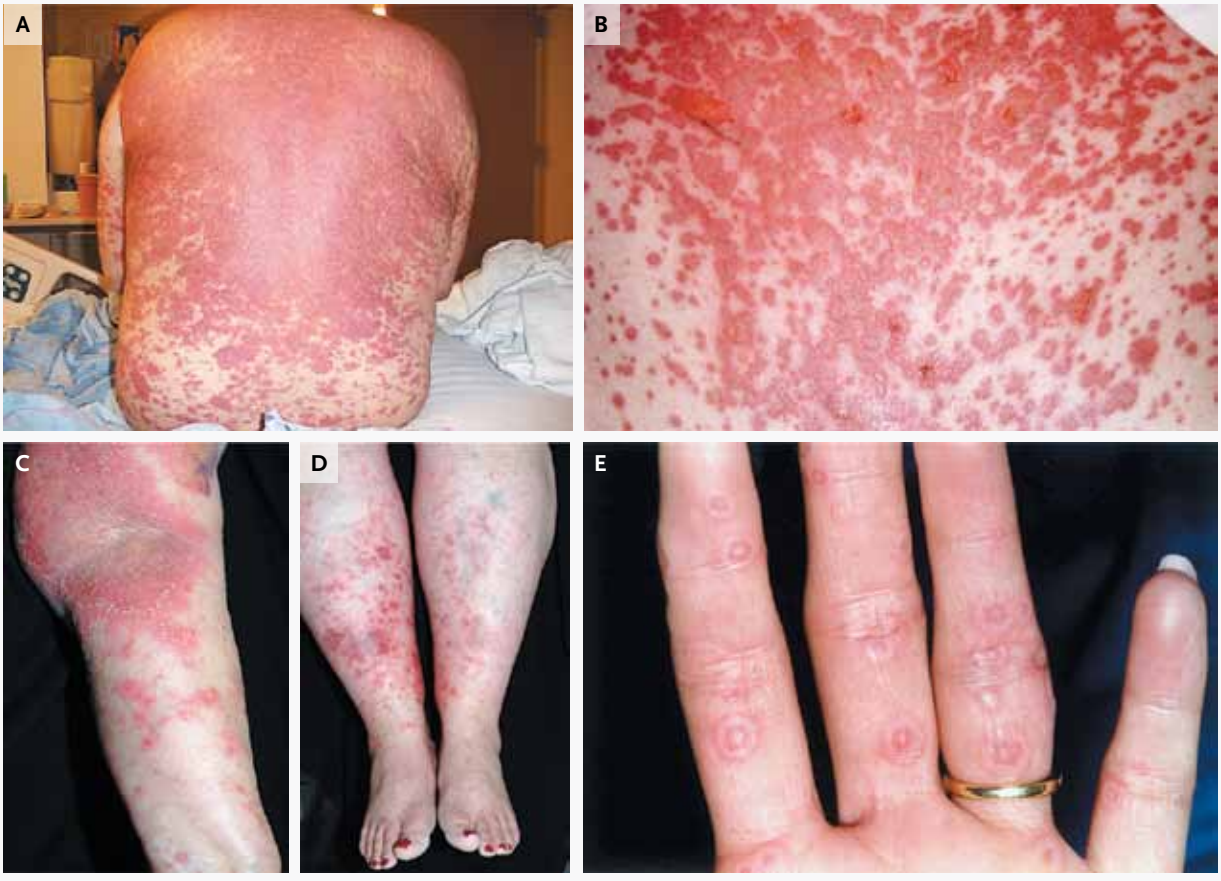

Figure 2. Clinical Presentations of Severe Cutaneous Reactions to Drugs.

Panel A shows indurated, deep-red-to-violaceous macules and papules coalescing to form plaques in a patient who had drug rash with eosinophilia and systemic symptoms (DRESS). Panel B shows widespread, bright-red edematous papules and plaques with early blistering in a patient with Stevens–Johnson syndrome. Some of the lesions are purpuric. Panel C shows acute generalized exanthematous pustulosis with small pustules, most of which are concentrated on the periphery of an erythematous plaque in a flexural area (e.g., axilla), and scattered papules and plaques, some with pustules. Panel D shows erythematous lesions in a patient with the early phase of cutaneous vasculitis. The lesions did not completely blanch and became purpuric within a few days. Panel E shows true target lesions characteristic of erythema multiforme that is not usually due to drugs. The lesions have three zones: an erythematous or dusky central papule, an edematous middle ring, and an erythematous outer ring. True target lesions are not usually seen in cases of Stevens–Johnson syndrome and toxic epidermal necrosis that are due to drugs.

delayed hypersensitivity reaction. However, standardized reagents for patch testing are lacking, and sensitivities below 10% have been reported.[40] The lymphocyte transformation test attempts to quantify in vitro activation of T cells in response to a drug or its metabolites, but the test is cumbersome and not sufficiently standardized for clinical decision making.[40] Drug provocation testing relies on the controlled readministration of a suspected drug to determine causality. Such testing is rarely used in clinical practice because it is not well standardized, may have false positive or false negative results, and carries a risk of triggering a new and possibly more serious drug reaction.

Skin biopsy may help identify SJS–TEN or AGEP in their early phases, but specific histopathological features that would distinguish exanthematous eruptions from DRESS and viral exanthems early in their course are lacking.[41] Phototoxic reactions have characteristic features on biopsy.

MANAGEMENT

Whenever feasible, identification and prompt withdrawal of the suspected drug constitute the cor-

nerstone of management for drug-induced eruptions. This is particularly important for drugs with a short half-life (<24 hours) when an exanthematous rash may represent the early sign of SJS–TEN, since prompt withdrawal of drugs with a short (but not long) half-life has been associated with reduced mortality.[42] Patients with signs and symptoms suggesting that the rash may be an early manifestation of a severe reaction should be closely monitored and are often hospitalized until a severe reaction can be ruled out. If the drug is essential and the reaction is not severe, desensitization after recovery may be attempted, but this process is rarely required and is cumbersome.

Sedating antihistamines such as diphenhydramine and hydroxyzine may provide symptomatic relief from pruritus. Potent topical glucocorticoids (which should not be used on the face or in intertriginous areas) may reduce signs and symptoms of the rash, but data from randomized trials of their efficacy in this setting are lacking. Data from a retrospective review and an open-label study, respectively, suggest that early treatment of SJS–TEN with systemic glucocorticoids or cyclosporine is associated with reduced mortality.[43,44] The role of intravenous immune globulin in the treatment of SJS–TEN is controversial. The benefits of systemic glucocorticoids relative to their risks in the treatment of exanthematous drug reactions are not clear.

SUBSEQUENT CARE OF PATIENTS WITH A HISTORY OF AN EXANTHEMATOUS DRUG REACTION

Although in many patients, rechallenge with a drug thought to be responsible for a prior drug-related rash does not result in a new eruption, it should generally be avoided because an eruption on reexposure to the drug may be more severe than the previous eruption. The exception is infectious mononucleosis; if a rash develops in association with the use of aminopenicillin in a patient with this disorder, the risk associated with readministration is only slightly higher than it is for first-time users of the drug.

Exposure to chemically related compounds is also a concern among patients with a prior drug exanthem. However, in many cases, the related drug is tolerated. Among patients who have had an exanthematous (non-IgE–mediated) rash in association with a penicillin antibiotic, the risk of a reaction to a beta-lactam antibiotic is probably less than 10%, and cross-reactivity between cephalosporins with different side chains is infrequent.[45] Sulfonamide antimicrobial agents are frequent causes of drug eruptions. The structures of nonantimicrobial sulfonamides, including diuretics, some NSAIDs, and antidiabetic agents, differ sufficiently from the structures of sulfonamide antibiotics that cross-reactivity with sulfonamide antibiotics is unlikely.[46] Cross-reactivity is frequent among aromatic amine antiepileptic agents.[47] Irrespective of the agent causing an initial drug reaction, persons with a history of drug hypersensitivity are about twice as likely to have hypersensitivity reactions to any other medication as are those without such a history.[46]

AREAS OF UNCERTAINTY

Limited information suggests that HLA haplotypes and other genetic factors may be useful in predicting the risk of exanthematous reactions to certain drugs, but more data are needed to improve the identification of persons at high risk for such reactions. In addition, a better understanding is needed of factors that mediate differences in the extent and severity of exanthematous drug reactions among affected patients exposed to the same medication. Finally, the usefulness of systemic glucocorticoids and other treatments for exanthematous drug reactions remains uncertain.

GUIDELINES

Guidelines for the identification and management of cutaneous drug reactions have been published by the American Academy of Dermatology (most recently in 1996)[48]; the American Academy of Allergy, Asthma, and Immunology[49]; and the British Society for Allergy and Clinical Immunology.[50] The British guidelines put greater emphasis on skin testing to determine causative drugs than do the recommendations presented here, which are otherwise consistent with these guidelines.

CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette almost certainly has an exanthematous drug eruption due to lamotrigine. Fortunately, she has no signs or symptoms suggestive of a severe cutaneous reaction, but she should be informed that if fever, mucosal symptoms, blisters, or malaise develops, she should seek immediate medical attention. She should also be advised to stop taking

lamotrigine and to ask her psychiatrist to prescribe an alternative agent that is not an aromatic amine. Since lamotrigine has a long half-life, the patient should be informed that the eruption may take a week or longer to fade. I would recommend that she apply emollients and take sedating antihistamines at bedtime. If the rash is very itchy, I would recommend treatment with a potent topical glucocorticoid for 1 week; although data from randomized trials are lacking, clinical experience suggests that this treatment should reduce secondary skin inflammation and pruritus. Oral glucocorticoids are not indicated, and no further tests are necessary. She should be counseled to avoid this drug and other aromatic amines, including phenytoin and carbamazepine.

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Supplementary Appendix

This appendix has been provided by the author to give readers additional information about his work.

Supplement to: Stern RS. Exanthematous drug eruptions. N Engl J Med 2012;366:2492-501.

Appendix

Exanthematous Drug Reactions

No. 11-04080

Robert S. Stern

Table of Contents

Table S1. Selected drugs associated with increased risk of the most common severe adverse cutaneous reactions * with level of risk and HLA types associated with increased risk in specific patient populations and drugs.

Drug-specific HLA associations	**DRESS (Drug Rash with Eosinophilia and Systemic Symptoms)**		**SJS/TEN (Stevens Johnson Syndrome/Toxic Epidermal Necrolysis)**		**AGEP (Acute Generalized Exanthematous Pustulosis)**
Anti-infective	**Risk Level**	**Associated HLA**	**Risk Level**	**Associated HLA**	**Risk Level**
Abacavir	SA	HLA-B*5701†			
Aminopenicillins	SA	HLA-A2 ‡	Mid		High
Cephalosporins	SA		Mid		
Hydroxychoroquine					High
Macrolides			Mid		High
Nevirapine	SA	HLA-DRB*0101†, HLA-Cw8 §, HLA-B*3501†	High		

		HLA-B*3505†			
Pristamycin					High
Sulfonamides	SA	HLA-A29	High	HLA-B12	Mid
				HLA-A*29	
Tetracyclines			Mid		
Quinolones			Mid		High
Anti-seizure					Mid¶
Carbamazepine	High	HLA-A*3101†	High	HLA-B*3101+	
				HLA-B*1502 ‡,	
				HLA-B* 5901§	
Lamotrigine	High		High	HLA-B*3801	
Phenobarbital	High		High		
Phenytoin	High		High	HLA-B*1502 ‡	
Other drugs					
Allopurinol	SA	HLA-B*5801 ‡	High	HLA-B*5801 †,‡	

Diltiazem				High
NSAID: Oxicam		High	HLA B*7301	Mid
			HLA-A2,B12	
NSAID: Acetic Acid		Mid		
Sulfasalazine	SA	High		High
Sertraline		High		
Terbinafine				High

References 1-18

* Quantitative risk estimates from case control and/or population based studies of patients are available for SJS/TEN and AGEP. For DRESS, quantitative risk estimates were identified for only antiseizure medications. They are more than 500 case reports reporting many drugs not assessed in Table S1 as possible causes of severe adverse cutaneous reaction to drugs.

High=point estimate relative risk ≥ 10 and significant and/or incidence ≥1 per 10,000 users.

Mid=point estimate of relative risk ≥ 5 and < 10 and significant.

SA=Suspected association based on detection of genetic association of increased risk of hypersensitivity reactions to this drug which is highly likely to include cases of DRESS with this drug or ≥ 5 suspect cases in review (2) and or case series (16, 17).

†Whites

‡Han Chinese and/or other non-Japanese Asians

§Japanese

¶ pooled estimate for all antiepileptic drugs listed below

Table S2. Algorithm for Assessing Relative Likelihood that Suspect Drug Caused an Exanthematous Eruption

Criterion	**Values**	**Rules to Apply**	**Possible Scores**
Delay from initial drug component intake to onset of reaction (index day)	Suggestive +3	From 4 to 14 days	-3 to 3
	Compatible +2	From 14 to 28 days	
	Possible +1	From 1 to 4 days, 28-56 days	
	Unlikely -1	>56 days	
	Excluded -3	Drug started on or after the index day*	
		In case of previous reaction to the same drug, only changes for: Suggestive +3: from 1-14 days Likely +1: from 15 to 56 days	
Drug present in the body on index day	Definite 0	Drug continued up to index day or stopped at a time point less than five times the elimination half-life before the index day	-3 to 0
	Doubtful -1	Drug stopped at a time point prior to the index day by more than five times the elimination half life but liver or kidney function alterations or suspected drug interactions are present	
	Excluded -3	Drug stopped at a time point prior to the index day by more than five times the elimination half-life, without liver or kidney function alterations or suspected drug interactions	

Prechallenge/rechallenge	Positive specific for disease and drug: 4	Rash after use of same drug	-2 to 4
	Positive specific for disease or drug: 2	Rash after use of similar drug or other reaction with same drug	
	Positive unspecific: 1	Similar reaction after use of any drug	
	Not done/unknown: 0	No known previous exposure to this drug	
	Negative -2	Exposure to this drug without an reaction (before or after reaction)	
Dechallenge	Neutral 0	Drug stopped (or unknown)	-2 to 0
	Negative -2	Exposure to this drug without reaction (before or after reaction)	
Type of drug (notoriety)	Associated 2	Drug with definite risk according to previous studies	0 to 2
	Unknown 0	All other drugs including newly released ones	
Other drug causes		Rank all drugs from highest to lowest intermediate score (total of all previous scores) If at least one has an intermediate score >3, subtract 1 point from the score of each of the other drugs with score < 3 taken by the patient (another drug is more likely)	
Final score -12 to 10. with <0, Very unlikely; 0-1, unlikely; 2-3 possible; 4-5, probable; ≥6, very probable			

Adapted from reference[18].

*Index Day=Day of the First Sign or Symptom of the Cutaneous Drug Reaction

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